Southern African HIV Clinicians Society
3rd Biennial Conference
13 - 16 April 2016
Sandton Convention Centre
Johannesburg

Our Issues, Our Drugs, Our Patients

www.sahivsoc.org
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WHAT A HEADACHE!

J. Nel
April 2016
HISTORY

- 34-year-old female
- Presented with an 18-month history of headaches.
  - Bilateral, frontoparietal
  - Refractory to simple analgesia
  - Occur daily – no respite over past 18 months
- Headaches had gradually worsened over the months, to the point where the patient was in tears due to the pain.
HIV HISTORY

- Commenced on 3TC/d4T/EFV from June 2006.
- Defaulted ARVs after clinic visit in October 2006.

- Returned to care in April 2008. Restarted on 3TC/d4T/NVP at that time. CD4=54.
  - Unclear why NVP substituted for EFV, but probably due to EFV side-effects that patient complained of.
HIV HISTORY

- May 2009: viral load 4100 copies/mL.
- August 2009: viral load 5000 copies/mL.
- September 2009: virological failure diagnosed and patient enrolled in CHRU Directly Observed Treatment study → changed to 3TC/TDF/LPVr in October 2009.
- Good response: viral load declined from 21 300 to LDL by Feb 2010, and remained totally suppressed until study ended in November 2010:
VIRAL LOAD PATTERN

3TC, d4T, NVP

3TC, TDF, LPV/r

Viral load

Sept-08
Oct-08
Nov-08
Dec-08
Jan-09
Feb-09
Mar-09
Apr-09
May-09
Jun-09
Jul-09
Aug-09
Sep-09
Oct-09
Nov-09
Dec-09
Jan-10
Feb-10
Mar-10
Apr-10
May-10
Jun-10
Jul-10
Aug-10
Sep-10
Oct-10
Nov-10

1
10
100
1000
10000
100000
1000000
10000000

340000
644
100
1000
10000
100000
1000000
10000000

3TC, d4T, NVP

3TC, TDF, LPV/r
Patient returned to TLC after study completion. Subsequent viral loads showed gradual deterioration of control however.

Patient admitted to missing the evening doses of her medications, and was formally counselled and moved to the “3rd line clinic” for closer supervision.
  - Patient’s mother reported that the patient had poor memory, and was forgetting to take her medications as a result.

Viral load did improve on counselling (153 copies/mL) and the patient was moved out of 3rd line clinic again.

Viral loads again showed upward trend over subsequent months, but had suppressed again by the time of admission.
VIRAL LOAD PATTERN (CONT.)

1-Nov  549  Oct-11  1343  Aug-12  480  Dec-12  736  Nov-13  603  May-14  759  Oct-14  Dec-14  Jan-15
OTHER HISTORY

- Previous pulmonary TB:

- Herpes zoster Feb 2014.
  - No residual neurology.

- Chronic hepatitis B
  - First diagnosed in September 2009
OTHER HISTORY

- Lives in Meadowlands, Soweto in a house with full amenities. Lives with uncle, grandmother, daughter, cousin and brother.

- Employed as a cleaner since 2010. Highest education level attained: Grade 11. Dropped out due to financial difficulties.

- No obvious animal exposures.

- No allergies.

- No illicit drug usage.

- Smoker: 10 pack year history
EXAMINATION

- BP 124/73
- P 103
- RR 16
- Temp 36.3°C
- Miserable-looking, in pain.
- BMI 28.9 kg/m²
EXAMINATION

- **Chest**: clear, normal vesicular sounds, no distress

- **CVS**: JVP normal, normal heart sounds, not in failure

- **Abdo**: SNT, no masses, no HSM, normal bowel sounds
**EXAMINATION**

- **Neuro**:  
  - GCS 15/15  
  - Tearful, unhappy  
  - Sometimes slightly irrelevant answers to questions  
  - Slow to respond  
  - Cranial nerves normal  
  - Cerebellar exam normal  
  - Motor and sensory exams normal
# Basic Bloods

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WCC</td>
<td>3.38</td>
<td>Sodium</td>
<td>141</td>
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<tr>
<td>Hb</td>
<td>12.7</td>
<td>Potassium</td>
<td>3.7</td>
</tr>
<tr>
<td>MCV</td>
<td>91.5</td>
<td>Chloride</td>
<td>105</td>
</tr>
<tr>
<td>Platelets</td>
<td>297</td>
<td>Bicarbonate</td>
<td>24</td>
</tr>
<tr>
<td>Viral load</td>
<td>759</td>
<td>Urea</td>
<td>4.3</td>
</tr>
<tr>
<td>CD4</td>
<td>439</td>
<td>Creatinine</td>
<td>39</td>
</tr>
<tr>
<td>Viral load</td>
<td>LDL</td>
<td>CRP</td>
<td>&lt; 5</td>
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## Basic Bloods

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>Conj. bilirubin</td>
<td>3</td>
</tr>
<tr>
<td>Protein</td>
<td>73</td>
</tr>
<tr>
<td>Albumin</td>
<td>35</td>
</tr>
<tr>
<td>ALP</td>
<td>84</td>
</tr>
<tr>
<td>GGT</td>
<td>30</td>
</tr>
<tr>
<td>ALT</td>
<td>14</td>
</tr>
<tr>
<td>AST</td>
<td>14</td>
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## Lumbar Puncture Results

<table>
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<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Protein</strong></td>
<td>0.81</td>
<td>0.66</td>
<td>0.98</td>
<td>0.70</td>
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<tr>
<td><strong>Glucose</strong></td>
<td>2.4</td>
<td>2.7</td>
<td>2.3</td>
<td>2.5</td>
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<tr>
<td><strong>Polymorphs</strong></td>
<td>8</td>
<td>0</td>
<td>7</td>
<td>0</td>
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<tr>
<td><strong>Lymphocytes</strong></td>
<td>126</td>
<td>42</td>
<td>109</td>
<td>6</td>
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<tr>
<td><strong>Erythrocytes</strong></td>
<td>1</td>
<td>33</td>
<td>2</td>
<td>492</td>
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<tr>
<td><strong>CLAT/India Ink</strong></td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Fungal culture</strong></td>
<td>(N/A)</td>
<td>(N/A)</td>
<td>No growth</td>
<td>(N/A)</td>
</tr>
<tr>
<td><strong>Bacterial culture</strong></td>
<td>No growth</td>
<td>No growth</td>
<td>No growth</td>
<td>No growth</td>
</tr>
<tr>
<td><strong>GeneXpert</strong></td>
<td>(N/A)</td>
<td>(N/A)</td>
<td>(N/A)</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Extensive bilateral white matter hypodensities
NEUROPSYCHOLOGICAL TESTING

- Objectively and subjectively **depressed**. Teary at times.

- **Worked steadily but extremely slowly** and needed a lot of prompting and encouragement.

- **Deficits in sustaining attention** for simple processing tasks, difficulty with divided attention, and an inability to encode information for further processing. **Limited mental flexibility**.
  - This implies that she might have difficulty focusing her attention for long periods at a time and should be given clear and precise instructions while making sure she understands.
NEUROPSYCHOLOGICAL TESTING

- Difficulty with sequential processing, short term acquisition, retaining and retrieval of information. Poor immediate and delayed memory. Very little information gets consolidated and stored in her long term memory.

- Deficits in spatial abilities, non-verbal concept formation, simultaneous processing, perceptual abilities, construct abilities non-verbal problem solving and fine motor abilities.

- Deficits in frontal lobe functioning that may influence ability to respond to social cues. Needs a lot of encouragement to start and complete tasks.
MOCA – cognitive screening device designed to assess for mild cognitive impairment.

- Tests memory, attention, abstraction, visuo-construction skills and orientation.
- Cut-off score is 26/30.

- Our patient: 17/30. Lost points on each subdivision of the test – globally weak.
Becks Depression Inventory (BDI)

- 21 items assessing the patient’s feelings and symptoms of depression over a one week period.
- Maximum points = 63. Higher is worse. Scores of > 30 indicate severe depression.

- Our patient: 50/63: severe depression
STOP AND THINK
FURTHER BLOOD RESULTS

- TB Bactec (blood): Negative
- TB culture (sputum): Negative
- ANA: Negative
- RF: Negative
- ANCA: Negative
- TPHA (serum): Negative
FURTHER CSF RESULTS

- CSF TPHA: Negative
- CSF VDRL: Negative
- CSF cytology: no malignant cells
- CSF ADA: 0.6
- TB culture: Negative
- JC virus PCR: Negative
- HSV-1 and -2 PCR: Negative
MRI

Diffuse, bilateral, symmetrical white matter $T_2$ and FLAIR hyperintensities involving deep and subcortical white matter. No sparing of the cerebellum.

No mass effect or enhancement

Features suggestive of HIV encephalopathy. PML and ADEM less likely due to symmetrical, bilateral diffuse pattern demonstrated.
THE ANSWER

- **HIV viral load on CSF**: 14,000 copies/mL
- **Serum viral load** *lower than detectable limit*.
SO NOW WHAT?

Compartmentalised viral escape of HIV within the CSF
The patient was currently on 3TC, TDF and LPV/r.

- The serum viral load was suppressed.
- The CSF viral load was 14 000.

What can be done?
# CSF Penetration of ART

<table>
<thead>
<tr>
<th>Agent type</th>
<th>CNS penetration–effectiveness score</th>
<th>4 (very good)</th>
<th>3 (good)</th>
<th>2 (fair)</th>
<th>1 (poor)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4 (very good)</td>
<td>3 (good)</td>
<td>2 (fair)</td>
<td>1 (poor)</td>
</tr>
<tr>
<td>NRTI</td>
<td></td>
<td>Zidovudine</td>
<td>Abacavir</td>
<td>Didanosine</td>
<td>Tenofovir</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Emtricitabine</td>
<td>Lamivudine</td>
<td>Zalcitabine</td>
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<tr>
<td>NNRTI</td>
<td></td>
<td>Nevirapine</td>
<td>Delavirdine</td>
<td>Etravirine</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Efavirenz</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td></td>
<td>Indinavir/r</td>
<td>Darunavir/r</td>
<td>Atazanavir</td>
<td>Nelfinavir</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Fosamprenavir/r</td>
<td>Atazanavir/r</td>
<td>Ritonavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Indinavir</td>
<td>Atazanavir</td>
<td>r Saquinavir</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Lopinavir/r</td>
<td>Fosamprenavir</td>
<td>Saquinavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Saquinavir/r</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Tipranavir/r</td>
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<td></td>
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<td></td>
<td>Raltegravir</td>
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<tr>
<td></td>
<td></td>
<td>Entry inhibitors</td>
<td>Maraviroc</td>
<td></td>
<td>Enfuvirtide</td>
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<tr>
<td></td>
<td></td>
<td>Integrase inhibitors</td>
<td>Raltegravir</td>
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</tr>
</tbody>
</table>

**NNRTI**: Non-nucleoside reverse transcriptase inhibitor; **NRTI**: Nucleoside reverse transcriptase inhibitor; **PI**: Protease inhibitor.

Data taken from [91].

Source: Future Neurology © 2010 Future Medicine Ltd
SO WHAT REGIMEN WOULD YOU CHOOSE FOR THIS PATIENT?

Currently: virally suppressed on 3TC / TDF / LPV/r
### CSF HIV Genotype

Major NRTI mutation: M184V

<table>
<thead>
<tr>
<th>Drug</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>Green</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Orange</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Red</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Red</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Red</td>
</tr>
<tr>
<td>Abacavir</td>
<td>Red</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Green</td>
</tr>
</tbody>
</table>
CSF HIV GENOTYPE

Major NRTI mutations: Y181C, K219N

<table>
<thead>
<tr>
<th>Nevirapine</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td></td>
</tr>
<tr>
<td>Etravirine</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine</td>
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</tbody>
</table>
**CSF HIV GENOTYPE**

Significant PI mutations: L10F, M46I, T74S, L76V

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indinavir/r</th>
<th>Saquinavir/r</th>
<th>Nelfinavir</th>
<th>Fosamprenavir/r</th>
<th>Lopinavir/r</th>
<th>Atazanavir/r</th>
<th>Tipranavir/r</th>
<th>Darunavir/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Red</td>
<td>Green</td>
<td>Orange</td>
<td>Red</td>
<td>Green</td>
<td>Red</td>
<td>Green</td>
<td>Orange</td>
</tr>
</tbody>
</table>
SO, LET’S TRY THIS AGAIN...

2nd time lucky...
<table>
<thead>
<tr>
<th>Drug</th>
<th>CSF Penetration</th>
<th>CSF susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC/FTC</td>
<td>Green</td>
<td>Red</td>
</tr>
<tr>
<td>TDF</td>
<td>Red</td>
<td>Green</td>
</tr>
<tr>
<td>AZT</td>
<td>Blue</td>
<td>Yellow</td>
</tr>
<tr>
<td>ABC</td>
<td>Yellow</td>
<td>Green</td>
</tr>
<tr>
<td>d4T</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>EFV</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>NVP</td>
<td>Blue</td>
<td>Red</td>
</tr>
<tr>
<td>ETR</td>
<td>Green</td>
<td>Red</td>
</tr>
<tr>
<td>LPV/r</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>ATV/r</td>
<td>Yellow</td>
<td>Green</td>
</tr>
<tr>
<td>DRV/r</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>RAL</td>
<td>Green</td>
<td>Red</td>
</tr>
</tbody>
</table>
BUT WHAT IF THE SERUM HIV VIRUS STRAIN IS DIFFERENT?

Patient suppressed on 3TC/TDF/Aluvia
SO, LET’S TRY THIS ONE MORE TIME...

3rd time’s the charm!
SO, THE BEST COMBINED REGIMEN:

For The CSF:

<table>
<thead>
<tr>
<th>Drug</th>
<th>CSF Penetration</th>
<th>CSF susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPV/r</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3TC/FTC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

_and a little help from:_

3TC/FTC

For the serum:

3TC, LPV/r, RAL and maybe AZT
WHAT ARE WE MISSING?

OK, 4th time lucky…
For the chronic hep B:
- 3TC, TDF

For the HIV in the CSF:
- AZT, LPV/r, RAL ± 3TC

For the HIV in the serum:
- 3TC, TDF, LPV/r, RAL ± AZT

**Final regimen:** 3TC, AZT, TDF, LPV/r, RAL

Patient ended up on DRV/r instead of LPV/r due to intolerance (diarrhoea). Easy swap because same CSF effect and CSF susceptibility, and likely same or better serum susceptibility.
### FINAL LP — 4 MONTHS LATER

<table>
<thead>
<tr>
<th></th>
<th>July 2015</th>
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<tbody>
<tr>
<td>Protein</td>
<td>0.08</td>
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<tr>
<td>Glucose</td>
<td>3.0</td>
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<tr>
<td>Polymorphs</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>3</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td>0</td>
</tr>
<tr>
<td>CLAT/India Ink</td>
<td>Negative</td>
</tr>
<tr>
<td>Bacterial culture</td>
<td>No growth</td>
</tr>
</tbody>
</table>
HIV CONTROL

- Ever since the CSF-penetrating ARVs given:
  - Depression cleared
  - Headaches gone
  - Neurocognitive issues improved

- Patient’s serum viral load has been undetectable ever since switching regimens, despite having to take 5 ARVs.
  - This is the first time since the DOT trial that she has ever maintained viral suppression.
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